(5) Claims 10, 51, 52, and 56-57 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Norman (1991) (¶16).

Each of these rejections is respectfully traversed, as explained below.

The Telephone Interview

Applicants appreciate the Examiner's participation in the telephone interview of May 10, 2001. Applicants discussed a possible revision of the claims to avoid the issues now before us and proposed to amend the application accordingly. However, in light of the Examiner's subsequent disapproval of the Proposed Amendment, Applicants have withdrawn the Proposed Amendment and submit this Amendment. In this amendment, Claims 1, 9, 10, 14, 15, 18, 51, 52 and 55 have been amended, and Claims12, 13, 16, 23, 25-27, 54, 58 and 59 canceled.

The Present Invention

The inventors of the present application have made a remarkable new discovery -- that Rose Bengal and other halogenated xanthenes interact as radiosensitizers or radiosensitizer agents with ionizing radiation and thereby treat cancer and tumors. Applicants have discovered further combinations also claimed herein, but this broad combination has heretofore been completely unknown, so far as can be determined.

The primary references cited by the Examiner generally disclose Rose Bengal, a halogenated xanthene but, Applicants submit, not as a radiosensitizer nor as a radiosensitizer agent that interacts with ionizing radiation.

Radiosensitizers

The present application discusses halogenated xanthenes being useful as radiosensitizer agents to interact with ionizing radiation and treat cancers and tumors. The terms "radiosensitizer" and "radiosensitizer agent" are used throughout the specification of the present application, in a discussion of the goal of such agents to enhance the efficacy of ionizing radiation as a treatment for cancerous tumors, for example, and the success of the claimed agents. For example, the specification discusses "radiosensitizer" and "radiosensitizer agents" early in the application:

> "Others, however, have focused their efforts on developing agents that are sensitized or activated by the ionizing radiation mentioned above. Potentially, the use of such radiation would enable treatment of more deeply seated diseased tissue than that possible with optical radiation. The agents used with such radiation are known as radiosensitizers. It is also desirable to achieve preferential concentration of the radiosensitizer in the diseased tissue, either through natural processes or via localized application, so as to provide additional specificity relative to that achievable through standard radiation therapy. The desired result is for radiation to become more efficacious when the radiosensitizer is present in tissue, so that less radiation is needed to treat the lesion tumor or other diseased tissue, and, accordingly, potential damage to surrounding healthy tissue, resulting from collateral exposure to the radiation, is reduced."

Specification, page 2, lines 17-20 (emphasis added). Other citations occur on nearly every page thereafter in the specification. An on-line dictionary defines "radiosensitizer" as follows:

> "A radiosensitizer is a substance given to a patient to make the intended target (such as a tumor) more susceptible to the effects of radiotherapy."

BioTech Life Science Dictionary (Attachment A). Groenwald et al., A Clinical Guide to Cancer Nursing, p. 61-62 (1995) (Attachment B) states that radiosensitizers are in the class of "Chemical and thermal modifiers of radiation" and that such radiosensitizers "increase radiosensitivity of tumor cells" and "achieve greater cell kill". Groenwald et al. expanded on that in 1997 in Cancer Nursing Principles and Practice, 4th ed., p. 260-261 (1997) (Attachment C):

> "The goal of radiotherapy is to achieve maximum tumor cell kill while minimizing injury to normal tissues (therapeutic ratio). Efforts to improve the therapeutic ratio have resulted in development of certain compounds that act to increase the radiosensitivity of tumor cells...Combined modality therapy with both radiation and certain cytotoxic agents also takes advantage of enhanced tumor cell kill. Drugs...often are used along with radiation to achieve greater cell kill than either therapy could achieve if used independently. When used alone, chemical modifiers of radiation therapy (radiosensitizers), however, are not generally cytotoxic like the chemotherapeutic agents."

See also Balch et al., Cutaneous Melanoma, p. 399-400 (1998) (Attachment D).

Hence, not only are the terms "radiosensitizer" and "radiosensitizer agent" well defined in the present application, they are also terms which are clearly recognized and understood by those skilled in the art.

As explained in depth *infra*, none of the cited references in the Final Rejection disclose or suggest that a halogenated xanthene, in general, or Rose Bengal, in particular, is a radiosensitizer or radiosensitizer agent for use with ionizing radiation.

Also, as indicated by the above citations in BioTech Life Sciences Dictionary, Groenwald et al., and Balch et al., it is clear to those skilled in the art that the radiosensitizers or radiosensitizer agents described in the present invention are agents or medicinal drugs that are administered to patients in order to improve the efficacy of radiation therapy.

FDA Regulations

The U.S. Food and Drug Administration ("FDA") carefully regulates interstate commerce in all such agents or medicinal drugs approved for human use in the U.S. The FDA has strict labeling requirements (Attachment E) concerning identification of the manufacturer, directions for use, ingredients, and intended use for any drug sold in interstate commerce. For example, concerning

identification of manufacturer, 21 CFR §201.1 ("Drugs; name and place of business of manufacturer, packer, or distributor") states:

> "(a) A drug or drug product (as defined in Sec. 320.**1** of this chapter) in finished package form is misbranded under section 502 (a) and (b)(**1**) of the act if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor..."

Further, 21 CFR §201.5 ("Drugs; adequate directions for use") requires detailed labeling concerning drug usage and dosage:

> "*Adequate directions for use* means directions under which the layman can use a drug safely and for the purposes for which it is intended. (Section 201.128 defines "intended use.") Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of:
>
> (a) Statements of all conditions, purposes, or uses for which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.
>
> (b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
>
> (c) Frequency of administration or application.
>
> (d) Duration of administration or application.
>
> (e) Time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).
>
> (f) Route or method of administration or application.
>
> (g) Preparation for use, i.e., shaking, dilution, adjustment of temperature, or, other manipulation or process." (Emphasis in original)

Concerning quantitative, definitive identification of drug ingredients, 21 CFR §201.10 ("Drugs; statement of ingredients") states:

> "(a) The ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, ...

(b) The term *ingredient* applies to any substance in the drug, whether added to the formulation as a single substance or in admixture with other substances..." (Emphasis in original)

Finally, concerning intended use (i.e., indications) for a drug, 21 CFR §201.128 ("Meaning of 'intended uses' ") states:

> "The words *intended uses* or words of similar import in Secs. 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives." (Emphasis in original)

Therefore, any drug product, such as a radiosensitizer agent, will, within all jurisdictions of the U.S. (i.e., all jurisdictions falling under the auspices of the U.S. FDA, as well as those of the U.S. PTO), be strictly regulated by the FDA, and will require detailed labeling concerning manufacturer, composition and intended use. As such, the commercial non-drug channels for a reagent grade material (for example reagent grade Rose Bengal from a chemical supply house, such as for example Sigma Chemical, used for laboratory, industrial or cosmetic purposes) will be completely distinct from those for any drug or drug product (for example a radiosensitizer agent approved for use in the U.S., which must comply with FDA regulations concerning drugs and drug products).

Accordingly, the granting of Applicants' claims for a radiosensitizer agent for treatment of cancer and tumors, said radiosensitizer agent comprising a halogenated xanthene and interacting with ionizing radiation applied to said cancer or tumor to enhance the therapeutic efficacy of said ionizing radiation, will in no way impact commercial trade in non-drug compositions of the halogenated xanthenes, nor will it affect any other *non-radiosensitizer medicinal use* of the halogenated xanthenes

(for example, as described *infra*, use of radiolabelled Rose Bengal for diagnosis of liver disease, which will clearly require very different labeling concerning intended use, will be unaffected).

The Claims

The present claims are not directed merely to halogenated xanthenes in general, and Applicants readily concede that halogenated xanthenes are known substances. That has not been contested by Applicants. Instead, the claims are directed to novel and non-obviousness combinations which include halogenated xanthenes for specific medicinal purposes.

Claim 1, for example, is for a combination of the following:

- a radiosensitizer agent comprising a halogenated xanthene;
- interacting with ionizing radiation applied to a cancer or tumor;
- to enhance the therapeutic efficiency of the ionizing radiation.

This claim therefore is not promulgated with the objective of prohibiting all commerce in halogenated xanthenes, but only to obtain the patent right to exclude halogenated xanthenes, as radiosensitizer agents, in combination with ionizing radiation applied to cancers and tumors, for enhancing the therapeutic efficiency of ionizing radiation. As explained above, commerce of compounds (or substances) for cancer treatment is strictly regulated by the FDA, and as a result, specific pharmaceutical, drug or other medicinal products (such as the radiosensitizers of the present invention vs. the radiopharmaceuticals described by Serafini et al.) are easily distinguishable, commercial entities, even if they have some comparable active ingredients.

The PTO has recognized the patentability of methods using halogenated xanthenes that are disclosed in the instant application, and Applicants have paid the issue fee in the parent application in which claims are to issue for Applicants' new and nonobvious methods. Applicants assert in this

divisional application that they are entitled to patent rights for the substances (radiosensitizer agents comprising halogenated xanthenes) in particular combinations, all of which include ionizing radiation. Further, these claims are directed toward various such combinations for treatment of cancer and tumors.

As a result and as explained in more depth below, Applicants respectfully submit that the claims of the present application are clearly distinguishable and patentable over the cited references and should now be allowed.

I. The §102 Rejections

A. First §102 Rejection

The Examiner rejects Claims 1-3, 5-8, 12-13, and 58-59 under 35 USC §102 as being "inherently anticipated by Serafini et al. ... for reasons of record."[1] This rejection is respectfully traversed as the claimed invention and Serafini et al. are very different. This reference does not fully meet the claims. Applicants believe that with a further explanation, these differences will become clear to the Examiner. Applicants acknowledge the withdrawal of the §102 rejection of claims 10, 15-16, 23, and 51 based on Serafini et al. Final Rejection, page 5, ¶9.

The present invention, as recited in independent Claim 1and claims dependent thereon, is directed to a *radiosensitizer agent* for *treatment* of cancer and tumors, the radiosensitizer agent comprising a halogenated xanthene, and the radiosensitizer agent *interacting with ionizing radiation applied to* the cancer or tumor to enhance the therapeutic efficacy of the ionizing radiation.[2]

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[1] Applicants are canceling Claims 12, 13, 58 and 59.

[2] Applicants consider the amendment to Claim 1 not to be a Festo type narrowing amendment because the amendment clarifies what one skilled in the art would understand, i.e., that the radiosensitizer agent interacts with ionizing radiation applied to the cancer or tumor to

In contrast, Serafini et al. does not disclose or suggest

- a radiosensitizer agent,
- a radiosensitizer agent for treatment of cancer and tumors,
- a radiosensitizer agent comprising a halogenated xanthene radiosensitizer agent, or
- a radiosensitizer agent that interacts with ionizing radiation applied to the cancer or tumor to enhance the therapeutic efficacy of the ionizing radiation.

Merely because Serafini et al. discloses one use of Rose Bengal does not mean that it discloses any of the above items. As explained above, the FDA requires labeling for drugs, such as radiosensitizer agents, including information on intended uses. Hence, when any drug is sold as a radiosensitizer or radiosensitizer agent for treatment of cancers or tumors, its labeling will state that it is a radiosensitizer for treatment. This would apply to Rose Bengal or another halogenated xanthene sold as a radiosensitizer. As explained below, any Rose Bengal sold for use for the diagnostic purposes described in Serafini et al. would have a different labeling and thus be a different drug and distinctly different commercial entity.

Unlike the present invention, Serafini et al. describes the use of certain radioactive forms of Rose Bengal in the medical evaluation of liver function.[3] In a *diagnostic* test, a radioactive form of the compound (radiolabelled with iodine-131 or, as taught by Serafini et al., with iodine-123) is administered to the patient as an intravenous bolus. The subsequent distribution of the diagnostic agent throughout certain organs of the patient's body is then determined *by detecting the emissions*

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enhance the therapeutic efficacy of the ionizing radiation.

[3] Applicants note that the radiosensitizer agents comprising halogenated xanthenes, such as Rose Bengal, as claimed by the present invention are, typically, non-radioactive.

resulting from the spontaneous radioactive decay of the radioactive iodine contained in this radiolabelled Rose Bengal. Serafini et al. uses a radiation detection system (i.e., a "scintillation camera") that is placed outside the patient's body, for detecting this spontaneous radioactive decay of the radioactive iodine. (The scintillation camera receives and produces an electrical or other signal based on the detected radiation). Serafini et al. is thus concerned with an application in nuclear medicine where the intrinsic radioactivity of a substance is put to use. The substance in Serafini et al.'s case, Iodine-123-labeled-Rose Bengal, *emits* radiation which Serafini et al. reports on for imaging purposes. As seems appropriate, this article appears in a journal directed to nuclear medicine. Fundamentally, this reference indicates the advantage of one radioactive form of rose bengal over another, in forming images from the radioactive emissions.

In the Final Rejection, the Examiner states (¶17a) that Serafini et al. teaches Rose Bengal:

> "which has an inherent capacity to rapidly and efficiently concentrate into cellular molecules upon exposure to ionizing radiation; thus, a radiosensitizer or a pharmaceutical agent which in combination with ionizing radiation, finds use in treating diseased tissue with overall reduction in radiation exposure to treat diseases such as cancer or tumor. Specifically, Applicant claims a radiosensitizer agent, halogenated xanthene, a known product clearly taught by Serafini et al. and which has the inherent property to concentrate into diseased tissue (as shown by Serafini et al.). Therefore, the product of the present invention is concluded to be inherently anticipated by Serafini et al."

Applicants strongly but respectfully disagree with the Examiner's conclusion and note that the Examiner has made no specific citation to any disclosure in Serafini et al. where "concentrate[ing] into cellular molecules upon exposure to ionizing radiation" is shown. Nor has the Examiner shown a disclosure in this reference of using any halogenated xanthene to "treat diseases" or of a radiosensitizer agent for treatment of cancer and tumors. Indeed, the Examiner has not pointed out where halogenated xanthenes are identified as "a radiosensitizer agent."

In fact, Serafini et al. does not disclose or suggest a radiosensitizer agent[4] since no exogenous radiation is applied therapeutically, diagnostically or otherwise, to the tissue containing the Rose Bengal. The fact that Serafini et al. teaches that Rose Bengal could be tagged with radioactive Iodine-123 (page 630, col. 1) does not mean that Rose Bengal is a radiosensitizer. And the teaching that Iodine-123 can be a useful substitute for ^{131}I as a label for radiopharmaceuticals likewise is not a disclosure that Rose Bengal is effective as a radiosensitizer. Additionally, Applicants find no suggestion of any therapeutic modality in Serafini et al. Further, any radiation emanating from I-123 or I-131 that hits the tissue as a result of the radioactive decay of the imaging agent would not be regarded as therapeutically applied "ionizing radiation" by those skilled in the art.

Further, the reference teaches away from the invention. A central theme of Serafini et al. is the use I-123 instead of I-131 so as to *minimize the effects of spontaneously emitted radiation* to tissues containing diagnostic quantities of radiolabelled Rose Bengal (as well as to minimize or avoid damage to surrounding tissues and to tissues containing degradation products of such radiolabelled Rose Bengal). For example, in the abstract, Serafini et al. states:

> "The overall reduction in imaging time and radiation exposure...should greatly improve our diagnostic capabilities in evaluating the jaundiced patient."

In the second paragraph (p. 629), Serafini et al. states:

> "Because of the relatively high absorbed radiation dose produced by the beta decay and the 8-day half life of [radiolabelled] ^{131}I rose bengal, we are limited in the amount of activity [of radiolabelled rose bengal] that can be administered to the patient..."

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[4] Claim 1 specifically recites "A radiosensitizer agent" in the preamble. The Court of Appeals for the Federal Circuit has clearly stated that the preamble may be a limitation of the claim when it is required to confer meaning on the claim. Phillips Petroleum Company v. Huntsman Polymers Corp., 48 USPQ2d 1161 (Fed. Cir. 1998). This is true even when the preamble is stated in the form of "A _____ comprising". Id.

Finally, in the discussion (p. 631-632), Serafini et al. states:

> "Iodine-123 when compared with ^{131}I has several desirable physical properties.... The relatively short 13- hr half-life of ^{123}I decreases patient exposure [to radiation]..."

Thus, one of the fundamental concepts Serafini et al. is directed to is minimizing the effects of radiation in tissues containing Rose Bengal. This is completely the opposite of what is taught in the present invention, which seeks to *maximize the effects of ionizing radiation* in tissues containing Rose Bengal.

Applicants respectfully submit that the Examiner is not grounded in fact in suggesting that Serafini et al. teaches that Rose Bengal targets diseased tissue (such as that of cancerous tumors). Serafini et al. instead illustrates that retention of Rose Bengal in portions of the liver and gall bladder can be used to diagnose function of these particular organs. Specifically, anomalous patterns of retention of Rose Bengal, as illustrated by Figs. 1 and 2 of Serafini et al., can be used to identify and diagnose areas of abnormal excretion of Rose Bengal. In normal organs, Rose Bengal is expected to exhibit a characteristic concentration half-life and should exhibit substantially uniform distribution (i.e., isotropic distribution) throughout the organ. Upon intravenous administration, a bolus of Rose Bengal perfuses a given organ, then gradually washes out as the bolus is cleared from the blood stream (or in the case of the liver or gall bladder, the Rose Bengal is excreted through normal physiologic functions of the organ, for example into the bile). In a diseased liver or gall bladder, anisotropic retention in certain portions of the organ is characteristic of reduced excretory function of such portions. Accordingly, Rose Bengal, as used by Serafini et al., is not targeting these diseased portions, but instead is merely backing up in these portions (i.e., it is not being excreted through such portions at a normal rate). It is further noted that because it is based on backing up in certain blood

purifying organs, instead of targeting diseased tissue or tumors, only the liver and gall bladder are discussed in Serafini et al.

In short, this reference uses the radioactive quality of Iodine -123-Rose Bengal for diagnostic imaging -- just as its title states.

Therefore, for at least the above-stated reasons, there is no disclosure or suggestion in Serafini et al. of Rose Bengal or any other halogenated xanthene[5] in (1) a radiosensitizer agent, or (2) a radiosensitizer agent for any therapeutic treatment, or (3) a radiosensitizer agent that interacts with ionizing radiation applied to the cancer or tumor to enhance the therapeutic efficacy of the ionizing radiation. Serafini et al.'s use of Rose Bengal is completely different than the radiosensitizer agent of independent Claim 1 and in fact, appears to have almost no relevance to the present invention and the recited claims.

For the above-stated reasons, Applicants respectfully submit that the claims of the present application are neither anticipated nor obvious over Serafini et al.

B. Second §102 Rejection

Applicants acknowledge the withdrawal of the §102(b) rejection of claims 10, 15-16, 25, and 51 over Neckers. The Examiner continues the rejection of Claims 1-3, 5-9, 12-13 and 58-59 under 35 USC §102 as being "inherently anticipated by Neckers." Final Rejection, ¶10-11.[6] This rejection is also respectfully traversed, as Neckers is clearly different than the claimed invention.

The Examiner states that Neckers teaches Rose Bengal:

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[5] Serafini et al. mentions only Rose Bengal and does not disclose the use of any other halogenated xanthene.

[6]Applicants are canceling Claims 12, 13, 58 and 59.

> "which has an inherent capacity to rapidly and efficiently concentrate into cellular molecules upon exposure to ionizing radiation; thus, a radiosensitizer or a pharmaceutical agent which in combination with ionizing radiation, finds use in treating diseased tissue. Specifically, Applicant claims a radiosensitizer agent, halogenated xanthene, a known product clearly taught by Neckers and which has the inherent property to concentrate into diseased tissue. Therefore, the product of the present invention is concluded to be inherently anticipated by Neckers."

Final Rejection, ¶17(b), pp. 9-10. Applicants respectfully traverse the Examiner's conclusion, along with many of the Examiner's assertions concerning the facts about this reference.

Applicants submit that Neckers fails to provide any teaching of a radiosensitizer or a radiosensitizer agent. As explained *supra*, a radiosensitizer and radiosensitizer agent are clearly defined in the specification of the present application. Such a radiosensitizer or radiosensitizer agent is not found in Neckers.

Neckers, according to its own summary, reports and compares the optical properties, photochemical reactivity, and photophysical parameters of known derivatives of Rose Bengal. As such, it describes the many fundamental chemical and physical properties of the halogenated xanthenes, particularly Rose Bengal. Neckers mentions use "as a diagnostic probe," apparently in reference to Eosin. Neckers at page 3. Among other things, Neckers further mentions a "fluorescence spectrum" of a certain salt, noting that it has "a broad triad of peaks centered at 583nm (Table 3)." Id. at page 13. Neckers also mentions optical absorption and emission spectra, intermolecular energy transfer as measured by singlet oxygen yields, and intramolecular self-quenching. Id. at pages 18-21. A further discussion of quenching appears at pages 22-24.

The Examiner's assertion that Neckers discloses Rose Bengal as a radiosensitizer for use with ionizing radiation is not understood, and we respectfully submit, cannot withstand scrutiny. The term "radiosensitizer" is clearly defined in the specification of the present application and is well known

to those of ordinary skill in the art, yet Neckers fails to provide any teaching or suggestion of Rose Bengal as a radiosensitizer.

The Examiner's application of Neckers to support a Section 102 rejection is not based on a fair reading of the Neckers disclosure, we submit. For example, Applicants see no statement in Neckers that Rose Bengal or another halogenated xanthene would be useful as a radiosensitizer for ionizing radiation. The Examiner is respectfully requested to point out particularly the exact support from this reference for the proposition that these substances are radiosensitizers for such radiation.

Applicants find no teaching or suggestion in Neckers of a halogenated xanthene as a radiosensitizer agent.

In addition, Applicants find no disclosure in Neckers of interacting Rose Bengal or another halogenated xanthene with ionizing radiation.

Further, Applicants find no disclosure in Neckers of such agents for treatment of cancer or tumors or such agents that will interact with ionizing radiation applied to the cancer or tumor to enhance the therapeutic efficacy of the ionizing radiation, as required in the claims of the present application. So far as Applicants are aware, Neckers describes only the interaction of *optical* radiation (i.e., ultraviolet, visible and near infrared light), not *ionizing* radiation, with such agents.

The Examiner makes reference to Rose Bengal concentrating into cellular molecules upon exposure to ionizing radiation. To the extent that the Examiner relies on Neckers for this teaching, Applicants do not find that disclosure in the reference and respectfully ask the Examiner to identify its location so Applicants can consider it more fully.

In short, Applicants see nothing whatsoever in Neckers to indicate any application of any halogenated xanthene as a radiosensitizer or interacting it with ionizing radiation applied to cancers or tumors to enhance the therapeutic efficacy of the ionizing radiation. Merely identifying Rose

Bengal or other halogenated xanthenes as known compounds is far short of identifying them as radiosensitizers in the manner claimed, with ionizing radiation.

Applicants also note that Neckers is published in *J. Photochem. Photobiol.*, a journal that has a topical focus on the interaction of optical radiation (i.e., ultraviolet, visible and near infrared light) with matter, rather than on the interaction of x-rays, gamma-rays, and other high energy ionizing radiation with such matter. Such a journal is appropriate for the subject matter of Neckers, and is further indicative that Neckers concerns the interaction of *optical* radiation, not *ionizing* radiation, with Rose Bengal.

Accordingly, for the above-stated reasons, Neckers does not disclose or suggest the radiosensitizer agent of the claims of the present application, and the claims are clearly not anticipated by Neckers but are patentable thereover. Applicants therefore respectfully traverse the rejection of these claims over Neckers as an anticipating reference and request that such rejection be withdrawn.

II. §103 Rejections

A. First §103 Rejection

The Examiner also rejects Claims 4, 14, 18-20 and 25-27 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Khaw et al. Final Rejection, p. 6, ¶15 (first para.).[7] This rejection is respectfully traversed..

As explained above, neither Serafini et al. nor Neckers discloses nor suggests any radiosensitizer or radiosensitizer agent, and certainly does not disclose nor suggest the radiosensitizer

[7] Applicants propose to cancel Claims 25-27.

as claimed in the present application. As a result, even if these two references were combined[8], the combination still would fail to disclose or suggest a radiosensitizer agent comprising a halogenated xanthene, a halogenated xanthene radiosensitizer agent for any therapeutic treatment, or a radiosensitizer agent that interacts with ionizing radiation applied to the cancer or tumor to enhance the therapeutic efficacy of the ionizing radiation, as claimed in the present application. Adding Khaw et al. to the combination does not cure the shortcomings, for Khaw et al., as will be explained below, fails to disclose the features of Claim 1. As a result, the features of independent Claim 1 are patentably distinct over the hypothetical combination, wherefore all claims dependent thereon are patentably distinct also.

Rejected dependent Claims 4 and 14 concern targeting while rejected claims 18-20[9] concern other dependent features, encapsulation being one. This presumably is the reason for the citation of Khaw et al. Khaw et al. fails to disclose any of the claimed features of the present application. Instead, Khaw et al. discloses methods of manufacture and use of immunoliposomes (i.e., liposomes doped on their outside surface with an immunoactive moiety, such as an antibody). Such immunoliposomes are purported to provide means for targeted delivery of their contents to various immunologic targets (such as certain cancer cells) (see, e.g. col. 6, lns. 44-50). Use of such immunoliposomal delivery means is taught for use with therapeutic radioactive iodine (see col. 11,

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[8] Applicants do not admit that such a combination is proper. In fact, it is respectfully submitted that the only way that these references could be combined to arrive at the claimed invention is through the use of hindsight reconstruction using the claimed invention as a blueprint. The Court of Appeals for the Federal Circuit has held that such a combination is improper and cannot form the basis of a §103 obviousness rejection. *See* Ecolochem, Inc. v. Southern California Edison Company, 56 USPQ2d 1065, 1072-1076 (Fed. Cir. 2000)

[9] Applicants propose to cancel Claims 25-27 as being directed to the same subject matter as Claims 18-20. Likewise, Claim 54 is similar to Claim 4 and Claim 58 to Claim 2.

lns. 37-46) and for various "radiopaque" materials (see col. 11, lns 53-64). Specific examples of such use with contrast agents is given in Table I: Additional uses with radiosensitizing compounds is disclosed at col. 13, lns. 62-65. This is further discussed at col. 16, lns. 9-34 and lns. 52-60, and at col. 17, lns. 13-16.

Notably, Khaw et al. teaches that such delivery is based primarily on action of a specific affinity reagent (i.e., the immunoactive moiety) with specific intracellular antigens, as taught at col. 3, lns. 14-21. This fundamental concept is markedly different than the teachings of the present invention, which discloses new radiosensitizer agents (i.e., halogenated xanthenes) that exhibit intrinsic targeting for certain types of cells and tissues along with certain structural components of such cells and tissues (see, e.g. p. 6, ln. 12 - p. 7, ln. 23, of the present application). As a result, Khaw et al. teaches away from the subject matter of the present invention by requiring use of specific immunologic delivery means and liposomal packaging for successful transport and delivery of radiocontrast or radiosensitizer agents to diseased tissue. In contrast, in the present invention, such complex adjuvants are not required, but instead simple adjuvants (*e.g.*, simple liposomal formulations, rather than Khaw et al.'s more complex immunoliposomes) can be used in the formulation and optimization of such agents for certain physical targeting purposes (*see, e.g.* p. 7, lns. 17-21 of the present application). Thus, while Khaw et al. ***requires*** immunoliposomes for successful targeting and delivery of the liposomal contents, the present application does not have such a requirement, as this is not a limitation of the independent claims.

Further, Khaw et al. does not disclose or suggest the use of halogenated xanthenes as radiosensitizer agents.

Where none of the references in the hypothetical combination teach radiosensitizer agents that interact with ionizing radiation, combining them fails to produce the missing teachings. Even when

combined, these three references fail to disclose or suggest, either explicitly or otherwise, the radiosensitizer agent comprising a halogenated xanthene of the claims of the present application. Further, any combination of these references in an effort to reach the claimed invention is improper hindsight reconstruction.

Therefore, Applicants respectfully submit that the claims are patentable over these references.

B. Second §103 Rejection

Claims 15-16, 23 and 54-55 under 35 USC §103 stand rejected as being unpatentable over Serafini et al. or Neckers in view of Khaw et al. Final Rejection, p. 7, ¶15 (second para.).

These dependent claims concern other dependent features. Applicants propose to cancel Claims 16, 23 and 54 and keep Claims 15 and 55 concerning targeting moieties. For substantially the same reasons discussed above, these claims of the present application are patentable over the cited references for at least the reason that the parent claims are patentable over the hypothetical combination.

C. Third §103 Rejection

The Examiner also rejects Claims 10, 51, 52 and 56-57 under 35 USC §103 as being unpatentable over Serafini et al. or Neckers in view of Norman (1991)[10]. Final Rejection, p. 7, ¶16. This (new) ground of rejection is also traversed.

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[10] Applicants herein are amending the form of Claim 10 but not its substance. The amendment makes Claim 10 independent, including its base claim and the limitations previously made in that claim. These amendments were made to correct informalities in the claims and are not narrowing Festo type amendments.

As the Examiner recognizes, neither Serafini et al. nor Neckers discloses or suggests a radiosensitizer agent comprising a halogenated xanthene for treatment of cancer and tumors using ionizing radiation, wherein said halogenated xanthene is activated using x-rays having an energy greater than 30 keV (Claim 10) or wherein said ionizing radiation is approximately great than or equal to 1 keV and less than or equal to approximately 1000 MeV (Claims 51 and 52) or wherein said ionizing radiation is x-rays (Claim 56) and has an energy of between 30 kiloelectron volts and 1000 megaelectron volts. As a result, the Examiner cites Norman.

However, these references, even if combined[11], yield a combination that would still fail to disclose or suggest a halogenated xanthene radiosensitizer agent, a halogenated xanthene radiosensitizer agent for treatment or the use of applied ionizing radiation with such a radiosensitizer agent or a radiosensitizer agent with a halogenated xanthene for treatment of cancers and tumors, as claimed in the present application. As explained above, neither Serafini et al. nor Neckers discloses or suggests these features.

Norman also fails to disclose these features of the present invention. In fact, Norman actually teaches away from the claimed radiosensitizer agent of the present application in his teaching of three possible ways to increase the efficacy of radiosensitization: (1) irradiation at specific energies that are maximally absorbed by the radiosensitizer; (2) use of a novel agent with higher radiodensity (i.e., gadolinium); or (3) use of complex radiosensitizer conjugates that are directly incorporated into tumor cells (see "Discussion" on page S120 of Norman). In each of these elements, Norman teaches away from the subject matter of the claims of the present application.

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[11] Applicants do not admit that such a combination is proper.

In Norman's first example, he states that practitioners can use a specific activation energy of 32 keV but that such energy will have a poor penetration through the skull and brain to a tumor. Hence, Norman admits that this method is undesirable. Further, there is no teaching in this method of a halogenated xanthene, as in the claims of the present invention. In contrast to Norman, the present application teaches that the new halogenated xanthene class of radiosensitizer agents are compatible with a broad range of activation energies (see, for example, p. 9, line 20 - p. 10, line18). Thus, the halogenated xanthenes of the claimed invention do not suffer from these serious limitations on activation energy as taught by Norman.

In Norman's second example, he requires that practitioners use an exotic radiodense material, gadolinium. In contrast, the claims of the present application are directed to a halogenated xanthene which is a radiosensitizer agent which overcomes the shortcomings of earlier classes of radiosensitizers. Halogens (i.e., fluorine, chlorine, bromine, and iodine) and the claimed halogenated xanthenes as taught in the present application, are not exotic radiodense materials. Furthermore, Gadolinium is not a halogenated xanthene.

In Norman's third example, he teaches the use of complex radiosensitizer/nucleic acid conjugates for enhanced agent incorporation into target cells. However, Norman specifically states that such means are "a difficult and expensive method as compared to injecting [more radiosensitizer]." (p. S121) Thus, Norman teaches away from one of the benefits of the subject matter of the present application by recommending that practitioners *use more agent*, rather than *a better agent*. Further, Norman notes that a clear obstacle to proceeding with his method is toxicity to the patient! Hence, Norman appears to be admitting that this teaching is infirm.

In contrast, the halogenated xanthene radiosensitizer agents of the claims of the present application exhibit intrinsic targeting and incorporation into tumor and other diseased tissue (see, for

example, p. 6, line 13 - p. 7, line 23). Such intrinsic targeting does not require additional difficult or expensive methods for manufacture or use. Hence, these agents are far superior to those contemplated by Norman. Further, since the halogenated xanthene class of agent has a significant regulatory history and low agent cost (see p. 8, lines 2-4, of the present application), such agents do not have an expensive cost associated with their use in radiosensitization, as purported by Norman. Furthermore, numerous toxicology studies have shown that this class of agents (i.e., halogenated xanthenes) is non-toxic.

Thus, based on these substantive contradictions between the teachings of Norman and the claims of the present application, it is respectfully submitted that Norman would fail to motivate one of ordinary skill in the art to arrive at a radiosensitizer agent comprising a halogenated xanthenes as specifically claimed in the present application. Hence, such a combination is improper and infirm, as one skilled in the art would not combine Norman with either Serafini et al. or Neckers, and none of the references suggest such a combination, as required by the Court of Appeals for the Federal Circuit. Ecolochem, 56 USPQ2d at 1072-1076. This is particularly true where the art teaches away from the claimed invention. Id. at page 1075.

It is difficult to understand how a combination of references that nowhere disclose or suggest important features of the invention could suggest or lead the ordinary skilled artisan to the invention itself. Norman begins his discussion with the statement that iodinated contrast media (CM) enhance the radiation dose absorbed from diagnostic x-rays. Page S120, first sentence. He then mentions treating brain tumors. Id., second sentence. Norman says nothing about halogenated xanthenes in particular. Serafini et al. is concerned with scintillation photography using a radioactive form of Rose Bengal (a halogenated xanthene), but says nothing about using halogenated xanthenes as a radiosensitizer agent nor as x-ray contrast media. Neckers discusses optical properties of Rose

Bengal but again fails to suggest utility as a radiosensitizer agent. Since Serafini et al., Neckers, and Norman all fail to suggest halogenated xanthenes as a radiosensitizer agent for treating cancer and tumors and that the agent interacts with applied ionizing radiation for treatment of cancers or tumors, Applicants find no teaching from which these three references can be combined to arrive at the present invention. Certainly, Applicants see no prima facie showing by the Patent and Trademark Office which Applicants have to rebut. Further, Applicants submit that, even if these references could be combined arguendo, when combined none of them discloses or suggests this feature of the claimed invention. Hence, even when combined, they fail to disclose the claimed invention, and the invention would not have been obvious in view of such a combination.

Moreover, since the 1991 publication date indicated for Norman, seven years passed before the filing of the parent application in 1998, with no publication nor public use (so far as Applicants are aware) of using Rose Bengal or any other halogenated xanthene as a radiosensitizer for treating tumors or cancer tissue with ionizing radiation.[12] Given that cancer research is of global importance and focus, the passage of these several years following the publication of Norman, with no one appreciating the invention now claimed, is strong evidence of the non-obviousness of the claimed subject matter.

Accordingly, it is respectfully requested that this rejection be withdrawn.

III. §112 Rejection

In the Final Rejection, the Examiner rejects Claims 15-16, 23, 25-27 and 54 under 35 USC §112 as being indefinite. Applicants propose to cancel Claims 16, 23, 25-27 and 54.

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[12] Further, Applicants are unaware of any prior art suggesting use of the halogenated xanthenes as x-ray contrast media.

Applicants traverse the remaining objection to Claim 15 as it is believed that the claim is acceptable as written and passes muster under §112.

More specifically, the Examiner objects to Claim 15, stating that there is improper antecedent support for "to biologically sensitive structures". The Examiner suggests the language "to the" be added before this term. Initially, Applicants do not understand the Examiner's proposal and wonder if a typographical error was made. Further, it is submitted that the antecedent basis is correct in this claim. This term is being introduced for the first time in this claim and it is plural (i.e., "structures"). The exact language in the claim is "to biologically sensitive structures of said cancer or tumors" (referring to part of the cancer and tumors defined in independent Claim 1 for which this claim now depends). Therefore, it is respectfully submitted that this term is in correct form and that the claim is in an allowable form.

For the above-stated reasons, it is respectfully requested that the objections under §112 be withdrawn.

IV. Specification

Applicants propose to amend the specification to reflect the earlier application to which Applicants wish to claim priority. It is believed that no new matter is being added. Accordingly, it is requested that this proposed amendment be entered and allowed.

V. Request For Entry of Amendment

It is respectfully requested that this amendment be entered and considered. Applicants through an interview and other conversations with the Examiner have been earnestly attempting to place the application in a condition for allowance or appeal. Applicants submit that this amendment

places the application in a better condition for allowance or appeal. Accordingly, it is requested that this amendment be entered.

Conclusion

For the above-stated reasons, it is respectfully submitted that the claims of the present application are neither disclosed nor suggested by the cited references and are patentable thereover. Accordingly, it is requested that the claims be passed to allowance.

If the Examiner has any further questions or comments, please call Edward Manzo or the undersigned at 312-236-8500. If any fee should be due for this amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: June 27, 2001

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Marked up copies of claims amended herein:

1 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors [using radiosensitization or ionizing radiation], said radiosensitizer agent comprising a halogenated xanthene, said halogenated xanthene interacting with ionizing radiation applied to said cancer or tumor to enhance the therapeutic efficacy of said ionizing radiation.

4 (Twice Amended). The radiosensitizer agent of Claim 1 wherein said halogenated xanthene includes as a functional derivative [a] at least one targeting moiety selected from the group consisting of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, encapsulating vehicles short- or long-chain aliphatic or aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitriles, and azides.

5 (Twice Amended). The radiosensitizer agent of Claim 1 wherein said [radiosensitizer agent] halogenated xanthene also is an imaging contrast agent.

6 (Twice Amended). The radiosensitizer agent of Claim 5 wherein said [radiosensitizer] halogenated xanthene acts as an imaging contrast agent for computed axial tomography.

7 (Twice Amended). The radiosensitizer agent of Claim 5 wherein said [radiosensitizer] halogenated xanthene acts as an imaging contrast agent for X-ray imaging.

9 (Twice Amended). The radiosensitizer agent of Claim 1 wherein said [radiosensitizer agent is a] halogenated xanthene is selected from the group consisting of Phloxine B, Erythrosin B and Eosin Y.

10 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene [The radiosensitizer agent of Claim 1] wherein said halogenated xanthene is activated using x-rays having an energy greater than 30 keV.

Cancel Claims 12 and 13.

14 (Twice Amended). The radiosensitizer agent of Claim 1 [12] wherein at least one biological targeting moiety is attached to said [radiosensitizer agent] halogenated xanthene to enhance targeting of said [radiosensitizer agent] halogenated xanthene to biologically sensitive structures of said cancer or tumors.

15 (Twice Amended). The radiosensitizer agent of Claim 1 [12] wherein at least one chemical targeting moiety is attached to said [radiosensitizer agent] halogenated xanthene to enhance targeting of said [radiosensitizer agent] halogenated xanthene to biologically sensitive structures of said cancer or tumors.

Cancel Claim 16.

18 (Twice Amended). The radiosensitizer agent of Claim 1[4] wherein said halogenated xanthene is encapsulated [radiosensitizer agent is delivered by encapsulation of said radiosensitizer agent] in a delivery vehicle.

Cancel Claims 23 and 25-27.

51 (Twice Amended). A radiosensitizer agent for treatment of cancer and tumors using radiosensitization or ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene [The radiosensitizer agent of Claim 1] wherein said ionizing radiation is approximately greater than or equal to 1 keV and less than or equal to approximately 1000 MeV.

52 (Amended). The radiosensitizer agent of Claim 1[2] wherein said ionizing radiation is approximately greater than or equal to 1 keV and less than or equal to approximately 1000 MeV.

Cancel Claim 54.

55 (Amended). The radiosensitizer agent of Claim 1 wherein said halogenated xanthene includes as a functional derivative [a] at least one targeting moiety selected from the group consisting of hydrophilic and hydrophobic moieties.

Cancel Claims 58 and 59.